REMARKS

In the application, claims 2-4, 6-11, 12-15 and 23-33 are pending and rejected. After due consideration of the Examiner's comments in the Office Action of April 15, 2005, the claims have been amended to more clearly set forth what Applicants regard as their invention. Applicants respectfully request reconsideration of the claims as amended.

Rejections under 35 U.S.C. §112

The Examiner rejects claims 6 and 31 under 35 U.S.C. §112, 1st paragraph, as failing to comply with the written description requirement in that the claimed subject matter constitutes new matter.

The claims have been amended to more clearly reflect the procedure disclosed in the specification. In particular, the calculation of the background is described at page 25, beginning at line 10. This calculation is performed by selecting the measurements taken for a portion of the total number of probes that meet a pre-determined criterion. This can be the average hybridization intensity for "the lowest 5% to 10% of the probes in the array", " the lowest 5% to 10% of the probes for each gene", or the "probes that are not complementary to any sequence found in the sample", or it can be the "average signal intensity produced by regions of the array that lack any probes at all." Based on this description, the calculation of the background is claimed as "averaging the hybridization signals of a portion of the genes having a lowest signal intensity". Further, the value that is compared to the background is claimed as " the difference in hybridization signal intensity between each probe and its mismatch control." Support for this limitation is found at page 20, beginning at line 15. In view of the amendments to the claims, Applicants respectfully submit that the specification fully supports the subject matter as now claimed.

The Examiner rejects claims 2-4, 6-10, 23, 24, and 26-33 are rejected under 35 U.S.C. §112, 2nd paragraph, as being indefinite for recitation of the phrase "the hybridization signal of each gene in the set of genes to the compound of interest".

Claims 2 and 26 have been amended to eliminate the specified language.

Rejections under 35 U.S.C. §103

The Examiner rejects claims 2-4, 7-9, 11, 13, 14, 24-28, 30, and 32 under 35 U.S.C. §103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al.

Claims 11, 13 and 14 have been canceled. The foregoing amendments to the base claims (claims 2 and 26) have added further clarification of the steps of the inventive method. In particular, the step of identifying patterns in the profiles/expression data that demonstrate time stability and dose dependence, where the pattern is defined where the change in expression (up- or down-regulation) is in the same direction with time and increased dosage, has been included.

It is respectfully submitted that neither Cunningham et al. nor Hilsenbeck et al. teach or suggest using selection criteria in which gene expression data exhibits a particular pattern in response, where that pattern is both time and dose dependent and is consistent in the direction of change.

Cunningham et al. describe a method for screening a compound for toxicity by looking at specific genes to determine if the gene is upregulated or downregulated at least once during the time course. There is no evaluation based on dose. Further, there is no requirement of time stability such that a pattern is defined where the change in gene expression is in the same directions with time. Referring to the examples pointed out by the Examiner in Table 1, one gene is upregulated over time in all instances, while two are upregulated at some points in time and downregulated at others. In Table 2, the various genes are both upregulated and downregulated at various points in time, and in Table 3, there is both up- and downregulation at different times. The only criterion Cunningham et al. have set for designating a gene as a good indicator is that the gene was upregulated (or downregulated) at least three fold at least once over time. There is no requirement for time stability as claimed in the amended claims.

In addition to the absence of teaching of time stability and dose dependence, Cunningham et al. also do not teach use of a statistical method for identifying patterns and selecting subsets of genes that meet a pattern based on the two variables. Their sole criterion for "clustering", which is not statistical cluster analysis, is EST sequence. The

clusters consisted of genes that had overlapping EST sequences. Thus, there was only one variable used to group the genes, and this variable, sequence, had little to do with response and more to do with similarity of a particular gene's sequence to the sequences of genes that were already known to respond to a toxin. In the specific example cited by Cunningham et al., a large number of clusters (6,851) were identified. This still represents a large data set that needed to be considered. In contrast, Applicants' invention, by selecting only those genes that fit patterns of time stability and dose dependence, significantly reduces the number of genes that are subject to further consideration.

Hilsenbeck et al. do not disclose an analysis that relies on time stability and dose dependence. Hilsenbeck et al. are cited for their use of principal components analysis (PCA) in analysis of gene expression data at several time points to detect tamoxifin resistance. PCA is a widely used statistical factor analysis technique that reduces the number of variables and detects structure in the relationship between the variables. Applicants do not allege that their application of PCA to gene expression data is, in itself, novel. Nonetheless, it is submitted that using factor analysis, including PCA, to create one or more composite variables in the context of the entire claimed invention is novel. The method of Hilsenbeck et al. switches the variables and the observations, so that they have already selected the variables (three arrays, one for each of three tumor types) and many observations (genes in the array) to detect alterations of gene expression with time. This differs significantly from Applicants' invention because, in Applicants' method, there is a step prior to PCA in which genes are selected according to time stability and dose dependence. There would be no motivation to utilize PCA as taught by Hilsenbeck et al. to detect alterations with time because the data that is subjected to PCA analysis according to Applicants' method has already been selected to exhibit time stability.

The Examiner states that it would have been obvious to modify the method of Cunningham et al. using the method taught by Hilsenbeck et al. to vary dose as well as time of treatment, however, neither Cunningham et al. nor Hilsenbeck et al. teach or suggest variation of dose. Furthermore, neither Cunningham et al. nor Hilsenbeck et al. teach the creation of one predictive composite that is a binary value that is capable of

indicating positive or negative toxicological response to the compound of interest. As such, the procedure taught by Hilsenbeck et al. adds nothing to the procedure of Cunningham et al. that would be capable of rendering Applicants' invention obvious. Accordingly, it is respectfully submitted that the inventive method as now claimed is neither taught nor suggested by the combination of Cunningham et al and Hilsenbeck et al., and that the claimed invention is patentably distinct over the cited combination.

Claims 2, 11, 15, and 33 are rejected under 35 U.S.C. §103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. and in further view of Holden et al. Holden et al. are relied on for their teaching regarding the measurement of carbon tetrachloride toxicity as detected by gene expression.

It is submitted that Holden et al. do not impart to the combination of Cunningham et al. and Hilsenbeck et al. the missing subject matter needed to teach or suggest Applicants' invention. Specifically, Holden et al. do not teach or suggest selection of genes that fit patterns of time stability and dose dependence, creation of a set of composite variables, or the creation of one predictive composite that indicates toxicological response to the compound of interest. Accordingly the combination of the three references cannot render Applicants' invention obvious as now claimed.

The Examiner rejects claims 2, 10, 26, 28 and 29 under 35 U.S.C. §103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in further view of Machens et al. Machens et al. are relied on for their teaching of the use of logistic regression.

It is submitted that Machens et al. do not impart to the combination of Cunningham et al. and Hilsenbeck et al. the missing subject matter needed to teach or suggest Applicants' invention. Specifically, Machens et al. do not teach or suggest selection of genes that fit patterns of time stability and dose dependence, creation of a set of composite variables, or the creation of one predictive composite that indicates toxicological response to the compound of interest. Accordingly the combination of the three references does not render Applicants' invention obvious as now claimed.

Applicants' invention as now claimed is addressed to a method for generating a predictive composite that is indicative of toxicological response to a compound of interest. The method combines three separate statistical analysis steps to achieve the desired goal. Each of the references relied on by the Examiner teaches no more than a single statistical step to classify data, and none suggests the use of even two distinct steps, much less three distinct steps to convert gene expression data into a predictive composite. As stated in the specification at page 31, beginning on line 9 (as amended):

> The classification of objects into one or more groups based on many measurements has several well established techniques. These include discriminate analysis, logistic regression, multidimensional scaling, clustering, and neural networks. ... All of these methods work by making composite measures from the many measurements taken from each object. With gene expression patterns we have several time and dose points which represent multiple objects that are grouped together. None of these techniques is sufficient alone to represent this order of complexity. Contrast analysis allows us to identify measurements that are partially independent of time because they are time stable yet are affected by toxic doses more then non-toxic doses. The PCA combines these many measurements into a series of orthogonal composite measures. Since these composite measures are non-correlated by definition the problem of multi-colinearity which can decrease the power of logistic regression is eliminated. By combining these techniques in the order described, many of the limitations of each individual technique is reduced.

Thus, an important advantage provided by the present invention is the reduction of limitations experienced with individual statistical techniques that are widely used in the prior art, including those relied on by the Examiner. Applicants achieve this improvement by sequentially combining the steps of multi-variate analysis, factor analysis and logistic regression to produce one predictive value of toxicity. None of the cited references teach or suggest such a method.

In view of the foregoing Amendment and remarks, Applicants submit that all bases for rejection have been addressed and overcome such that the claims are allowable over the prior art. Accordingly, Applicants respectfully request that the Examiner withdraw all rejections set forth in the Office Action and issue a notice of allowance for all claims in the application.

Should the Examiner believe that the prosecution of this application might be expedited by further discussion of the issues, he is invited to telephone the undersigned attorney for Applicant at the telephone number indicated below.

Respectfully submitted,

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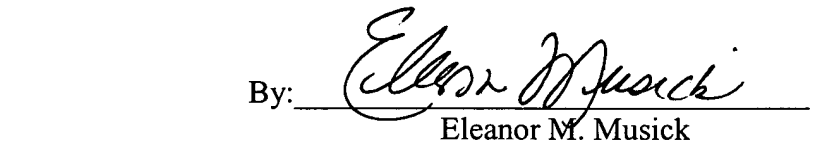
By: 

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